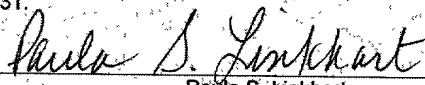


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 Paula S. Linkhart	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	§
<b>Marie-Ange BUYSE</b>	§
<b>Erwin SABLON</b>	§ Group Art Unit:
	§
Serial No.:	§ Examiner:
	§
Filed: <b>Herewith</b>	§ Atty. Dkt. No.: <b>INNS015—1</b>
	§ <b>11362.0015.DVUS01</b>
For: <b>INTERFERON-GAMMA-BINDING</b>	§
<b>MOLECULES FOR TREATING SEPTIC</b>	§
<b>SHOCK, CACHEXIA, IMMUNE DISEASES</b>	§
<b>AND SKIN DISORDERS</b>	§

**PRELIMINARY AMENDMENT**

**Box Patent Application**  
 Commissioner for Patents  
 Washington, DC 20231

Sir:

Prior to examination, please amend this application as follows:

**IN THE SUBSTITUTE SPECIFICATION:**

**At page 1, line 3, after the title, please replace the first paragraph with following new paragraph:**

--This is a divisional of co-pending application Serial No. 09/485,737 filed February 14, 2000, which is a § 371 national application of PCT/EP98/05165 filed August 14, 1998, which

claims priority under 35 U.S.C. §119 to EP 97 870122.5 filed August 18, 1997 and EP 98 870139.7 filed June 18, 1998.--

IN THE CLAIMS:

Please cancel claims 2-17 and 19 without prejudice to filing one or divisional applications.

**Please amend claims 1, 18, 20 and 21 to read as follows:**

1. (Amended) A molecule which binds and neutralizes interferon-gamma and which is chosen from the group consisting of:
  - a scFv comprising the humanized variable domain of the monoclonal antibody D9D10
  - a chimeric antibody comprising the humanized variable domain of the monoclonal antibody D9D10
  - a diabody comprising the humanized variable domain of the monoclonal antibody D9D10 and
  - a multivalent antibody.
18. (amended) A pharmaceutical composition comprising a molecule according to claim 1 or a mixture of said molecules in a pharmaceutically acceptable excipient.
20. (amended) A molecule according to claim 1 or a composition according to claim 18 for preventing or treating septic shock, cachexia, immune diseases such as multiple sclerosis and Crohn's disease and skin disorders such as bullous, inflammatory and neoplastic dermatoses.
21. (amended) A molecule according to claim 1 for determining interferon gamma levels in a sample.

**Please add new claims 22-39 as follows:**

- 22. (new) A method for neutralizing interferon-gamma activity in a mammal comprising administering to the mammal a pharmaceutically effective amount of a molecule that binds and neutralizes interferon-gamma, said molecule selected from the group consisting of:

a scFv comprising a humanized variable domain, wherein said variable domain comprises amino acids 1-117 and 133-239 of SEQ ID NO: 85;

a chimeric antibody comprising:

- a) a humanized heavy chain variable domain, said heavy chain variable domain having an amino acid sequence as shown in positions 1-117 of SEQ ID NO: 85, and
- b) the humanized light chain variable domain, said light chain variable domain having an amino acid sequence as shown in positions 133-239 of SEQ ID NO: 85;

a diabody comprising:

- a) a humanized heavy chain variable domain, said heavy chain variable domain having an amino acid sequence as shown in positions 1-117 of SEQ ID NO: 85, and
- b) a humanized light chain variable domain, said light chain variable domain having an amino acid sequence as shown in positions 133-239 of SEQ ID NO: 85; and,

a multivalent antibody, wherein said multivalent antibody is selected from the group consisting of a triabody, a tetravalent antibody, a peptabody, and a hexabody, and wherein said multivalent antibody comprises:

- a) a humanized heavy chain variable domain, said variable domain comprising amino acids 1-117 of SEQ ID NO: 85; and
- b) a humanized light chain variable domain, said variable domain comprising amino acids 133-239 of SEQ ID NO: 85.

23. (New) The method of claim 22, wherein said triabody further comprises:
- a) three variable domains of three different anti-interferon-gamma antibodies, or
  - b) at least one variable domain of an anti-interferon-gamma antibody in combination with
    - i) at least one variable domain of a different anti-interferon-gamma antibody, or
    - ii) at least one variable domain of an antibody which binds to another molecule excluding interferon-gamma;
- wherein at least one of the variable domains comprises amino acids 1-117 and 133-239 of SEQ ID NO:85.
24. (New) The method of claim 22, wherein said triabody further comprises three identical variable domains of an anti-interferon-gamma antibody.
25. (New) The method of claim 22, wherein said triabody further comprises three identical humanized scFvs, wherein each scFv has a zero residue linker joining the humanized heavy chain variable domain to the humanized light chain variable domain.
26. (New) The method of claim 22, wherein said tetravalent antibody further comprises:
- a) four variable domains of four different anti-interferon-gamma antibodies, or
  - b) at least one variable domain of an anti-interferon-gamma antibody in combination with
    - i) at least one variable domain of another anti-interferon-gamma antibody, or
    - ii) an antibody which binds to another molecule excluding interferon gamma;
- wherein at least one of the variable domains comprises amino acids 1-117 and 133-239 of SEQ ID NO:85.
27. (New) The method of claim 22, wherein said tetravalent antibody further comprises four identical variable domains of an anti-interferon-gamma antibody.
28. (New) The method of claim 22, wherein said tetravalent antibody further comprises four identical humanized scFvs as a homodimer of two identical molecules, each containing two humanized scFvs and a dimerization domain.

29. (New) The method of claim 22, wherein each said scFv comprises amino acids 1-239 of SEQ ID NO: 85.
30. (New) The method of claim 22, wherein said tetravalent antibody further comprises:
- a) a full-sized humanized antibody wherein said antibody comprises two heavy chains and two light chains, and
  - b) two humanized scFvs wherein each scFv is attached by its carboxy-terminus to a carboxy-terminus of one of said antibody's heavy chains, and wherein each said scFv comprises amino acids 1-239 of SEQ ID NO: 85.
31. (New) The method of claim 22, wherein said molecule is either a peptabody comprising five identical variable domains of an anti-interferon-gamma antibody, or a hexabody comprising six identical variable domains of an anti-interferon-gamma antibody.
32. (New) The method of claim 22, wherein said molecule is either a peptabody comprising five identical humanized scFvs, or a hexabody comprising six identical humanized scFvs.
33. (New) The method of claim 22, wherein each said scFv comprises amino acids 1-239 of SEQ ID NO: 85.
34. (New) The method of claim 22, wherein said molecule is either
- a) a peptabody comprising a combination of 1 to 4 variable domains from an anti-interferon-gamma antibody and, respectively, 4 to 1 variable domain(s) of an antibody which binds to another molecule other than interferon gamma, wherein at least one of the variable domains comprises amino acids 1-117 and 133-239 of SEQ ID NO:85; or
  - b) a hexabody comprising a combination of 1 to 5 variable domains from an anti-interferon-gamma antibody and, respectively, 5 to 1 variable domain(s) of an antibody which binds to another molecule other than interferon gamma, wherein at least one of the variable domains comprises amino acids 1-117 and 133-239 of SEQ ID NO:85.

35. (New) The method of claim 22, wherein the molecule is either:
- a) a peptabody comprising five variable domains from five different anti-interferon-gamma antibodies, wherein at least one of the variable domains comprises amino acids 1-117 and 133-239 of SEQ ID NO:85; or
  - b) a hexabody comprising six variable domains from six different anti-interferon-gamma antibodies, wherein at least one of the variable domains comprises amino acids 1-117 and 133-239 of SEQ ID NO:85.
36. (New) The method of claim 22, wherein the mammal is a human.
37. (New) The method of claim 22, wherein the mammal is afflicted with septic shock, cachexia, an auto-immune disease, or skin disorder.
38. (New) The method of claim 37 wherein the auto-immune disease is multiple sclerosis, Crohn's disease or rheumatoid arthritis.
39. (New) The method of claim 37, wherein the skin disorder is bullous, inflammatory or neoplastic dermatosis.--

## REMARKS

### I. Status of the Amendments

The parent application, U.S. Patent Application Serial No. 09/485,737 was allowed on October 10, 2001, but has not yet issued.

### Substitute Specification

Enclosed please find a substitute specification incorporating the amendment entered during the prosecution of the parent case SN 09/485,737:

- The amendments to the original Specification at pages 10 and 20 presented in the Preliminary Amendment of February 14, 2000;
- The priority claim regarding the national phase filing of the application on the first page of text;
- DNA/amino acid sequences within the application referenced with a separate sequence identification number; and
- The amendment to page 31 submitted on August 9, 2001.

No new matter has been added to the Substitute Specification. As required by 37 C.F.R. §1.125, a marked-up copy of the substitute Specification, showing the matter being added to and the matter being deleted from the Specification of record, is enclosed herewith.

#### **Amendments**

The substitute specification is amended herein to recite the relationship with the parent case.

Claims 2-17 and 19 have been cancelled. Claims 1, 18, 20 and 21 are amended. New claims 22-39 are added. Claims 1, 18, and 20-39 are now pending. The claims have been amended to delete recitation of multiple dependency and clarify the claimed subject matter. The new claims 22-39 are directed to methods of neutralizing interferon-gamma *in vivo* with the molecules delineated in the allowed claims of USSN 09/485,737. These new claims find support in the original specification of Serial No. 09/485,737, in particular pages 12, 16, 19, 22-27, 30-32, 37-49, 52-59, and 64-75; Figures 3, 4, 29, 30, 31, 32, and 33; and original claims 1-16. No new matter has been entered. A **Marked-Up Set of Claim Amendments** is attached.

## II. Sequence Listing

Please transfer the sequence information, including the computer readable form previously submitted ( July 18, 2001) in the co-pending application Serial No. 09/485,737 for use in this application, in accordance with the sequence Rules under 37 C.F.R. § 1.821(e).

## III. Conclusion

It is believed that no fee is due; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from Deposit Account No. 01-2508/11362.0015.DVUS01.

In view of the foregoing amendments, applicants respectfully submit the claims are in proper form and condition for allowance. Applicants request that the claims be allowed and the application advanced to issue.

The Examiner is invited to contact the undersigned attorney at (713) 787-1438 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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Reg. No. 29,775  
Attorney for Assignee  
INNOGENETICS N.V.

Howrey Simon Arnold & White, LLP  
750 Bering Drive  
Houston, TX 77057-2198  
(713) 787-1400

Date: February 7, 2002



## MARKED UP VERSION OF CLAIM AMENDMENTS

1. (Amended) A molecule which binds and neutralizes interferon-gamma and which is chosen from the group consisting of:
- a scFv comprising the humanized variable domain of the monoclonal antibody D9D10
  - a chimeric antibody comprising the humanized variable domain of the monoclonal antibody D9D10
  - a diabody comprising the humanized variable domain of the monoclonal antibody D9D10 and
  - a multivalent antibody
  - [– a ruminant antibody].
18. (amended) A pharmaceutical composition comprising a molecule according to claim 1 [any of claims 1–16] or a mixture of said molecules in a pharmaceutically acceptable excipient.
20. (amended) A molecule according to claim 1 [claims 1 to 16] or a composition according to claim 18 for preventing or treating septic shock, cachexia, immune diseases such as multiple sclerosis and Crohn's disease and skin disorders such as bullous, inflammatory and neoplastic dermatoses.
22. (amended) A molecule according to claim 1 [claims 1 to 16] for determining interferon gamma levels in a sample.
22. (New) A method for neutralizing interferon-gamma activity in a mammal comprising administering to the mammal a pharmaceutically effective amount of a molecule that binds and neutralizes interferon-gamma, said molecule selected from the group consisting of:
- a scFv comprising a humanized variable domain, wherein said variable domain comprises amino acids 1-117 and 133-239 of SEQ ID NO: 85;

a chimeric antibody comprising:

- a) a humanized heavy chain variable domain, said heavy chain variable domain having an amino acid sequence as shown in positions 1-117 of SEQ ID NO: 85, and
- b) the humanized light chain variable domain, said light chain variable domain having an amino acid sequence as shown in positions 133-239 of SEQ ID NO: 85;

a diabody comprising:

- a) a humanized heavy chain variable domain, said heavy chain variable domain having an amino acid sequence as shown in positions 1-117 of SEQ ID NO: 85, and
- b) a humanized light chain variable domain, said light chain variable domain having an amino acid sequence as shown in positions 133-239 of SEQ ID NO: 85; and,

a multivalent antibody, wherein said multivalent antibody is selected from the group consisting of a triabody, a tetravalent antibody, a peptabody, and a hexabody, and wherein said multivalent antibody comprises:

- a) a humanized heavy chain variable domain, said variable domain comprising amino acids 1-117 of SEQ ID NO: 85; and
- b) a humanized light chain variable domain, said variable domain comprising amino acids 133-239 of SEQ ID NO: 85.

23. (New) The method of claim 22, wherein said triabody further comprises:

- a) three variable domains of three different anti-interferon-gamma antibodies, or
- b) at least one variable domain of an anti-interferon-gamma antibody in combination with
  - i) at least one variable domain of a different anti-interferon-gamma antibody, or
  - ii) at least one variable domain of an antibody which binds to another molecule excluding interferon-gamma;

wherein at least one of the variable domains comprises amino acids 1-117 and 133-239 of SEQ ID NO:85.

24. (New) The method of claim 22, wherein said triabody further comprises three identical variable domains of an anti-interferon-gamma antibody.
25. (New) The method of claim 22, wherein said triabody further comprises three identical humanized scFvs, wherein each scFv has a zero residue linker joining the humanized heavy chain variable domain to the humanized light chain variable domain.
26. (New) The method of claim 22, wherein said tetravalent antibody further comprises:
- a) four variable domains of four different anti-interferon-gamma antibodies, or
  - b) at least one variable domain of an anti-interferon-gamma antibody in combination with
    - i) at least one variable domain of another anti-interferon-gamma antibody, or
    - ii) an antibody which binds to another molecule excluding interferon gamma;
- wherein at least one of the variable domains comprises amino acids 1-117 and 133-239 of SEQ ID NO:85.
27. (New) The method of claim 22, wherein said tetravalent antibody further comprises four identical variable domains of an anti-interferon-gamma antibody.
28. (New) The method of claim 22, wherein said tetravalent antibody further comprises four identical humanized scFvs as a homodimer of two identical molecules, each containing two humanized scFvs and a dimerization domain.
29. (New) The method of claim 22, wherein each said scFv comprises amino acids 1-239 of SEQ ID NO: 85.
30. (New) The method of claim 22, wherein said tetravalent antibody further comprises:
- a) a full-sized humanized antibody wherein said antibody comprises two heavy chains and two light chains, and
  - b) two humanized scFvs wherein each scFv is attached by its carboxy-terminus to a carboxy-terminus of one of said antibody's heavy chains, and wherein each said scFv comprises amino acids 1-239 of SEQ ID NO: 85.

31. (New) The method of claim 22, wherein said molecule is either a peptabody comprising five identical variable domains of an anti-interferon-gamma antibody, or a hexabody comprising six identical variable domains of an anti-interferon-gamma antibody.
32. (New) The method of claim 22, wherein said molecule is either a peptabody comprising five identical humanized scFvs, or a hexabody comprising six identical humanized scFvs.
33. (New) The method of claim 22, wherein each said scFv comprises amino acids 1-239 of SEQ ID NO: 85.
34. (New) The method of claim 22, wherein said molecule is either
  - a) a peptabody comprising a combination of 1 to 4 variable domains from an anti-interferon-gamma antibody and, respectively, 4 to 1 variable domain(s) of an antibody which binds to another molecule other than interferon gamma, wherein at least one of the variable domains comprises amino acids 1-117 and 133-239 of SEQ ID NO:85; or
  - b) a hexabody comprising a combination of 1 to 5 variable domains from an anti-interferon-gamma antibody and, respectively, 5 to 1 variable domain(s) of an antibody which binds to another molecule other than interferon gamma, wherein at least one of the variable domains comprises amino acids 1-117 and 133-239 of SEQ ID NO:85.
35. (New) The method of claim 22, wherein the molecule is either:
  - a) a peptabody comprising five variable domains from five different anti-interferon-gamma antibodies, wherein at least one of the variable domains comprises amino acids 1-117 and 133-239 of SEQ ID NO:85; or
  - b) a hexabody comprising six variable domains from six different anti-interferon-gamma antibodies, wherein at least one of the variable domains comprises amino acids 1-117 and 133-239 of SEQ ID NO:85.
36. (New) The method of claim 22, wherein the mammal is a human.

37. (New) The method of claim 22, wherein the mammal is afflicted with septic shock, cachexia, an auto-immune disease, or skin disorder.
38. (New) The method of claim 37 wherein the auto-immune disease is multiple sclerosis, Crohn's disease or rheumatoid arthritis.
39. (New) The method of claim 37, wherein the skin disorder is bullous, inflammatory or neoplastic dermatosis.